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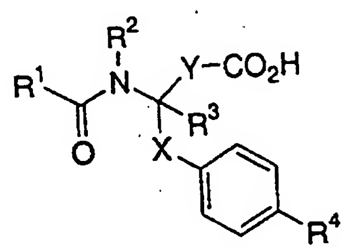
(54) Abstract Title
Aryl amides as cell adhesion inhibitors

(57) A method for the prevention or treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal comprises the administration of an effective amount of a compound of Formula I. The disease may be selected from asthma, allergic rhinitis, multiple sclerosis and inflammatory bowel disease. A method of preventing the action of VLA-4 integrin in a mammal comprises the administration of a compound of Formula I. A pharmaceutical composition comprises a compound of Formula I and a carrier.

Formula I



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TITLE OF THE INVENTION

AMIDES AS CELL ADHESION INHIBITORS

SUMMARY OF THE INVENTION

The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or $\alpha4\beta1$), the $\alpha4\beta7$ integrin (LPAM-1 and $\alpha4\beta_p$), and/or the $\alpha9\beta1$ integrin, thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin, $\alpha4\beta7$ to its various ligands, such as MadCAM-1, VCAM-1 and fibronectin, and /or $\alpha9\beta1$ to its various ligands, such as tenascin, osteopontin and VCAM-1. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4-, $\alpha4\beta7$–, and/or $\alpha9\beta1$–binding and cell adhesion and activation, such as AIDS-related dementia, allergic conjunctivitis, allergic rhinitis, Alzheimer's disease, aortic stenosis, asthma, atherosclerosis, autologous bone marrow transplantation, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, inflammatory bowel disease including ulcerative colitis and Crohn's disease, inflammatory lung diseases, inflammatory sequelae of viral infections, meningitis, multiple sclerosis, , multiple myeloma, myocarditis, organ transplantation, psoriasis, pulmonary fibrosis, restenosis, retinitis, rheumatoid arthritis, septic arthritis, stroke, tumor metastasis, type I diabetes, uveitis, vascular occlusion following angioplasty.

BACKGROUND OF THE INVENTION

The present invention relates to amide derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules (CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without

interfering with normal cellular functions is essential for an effective and safe therapeutic agent that inhibits cell-cell and cell-matrix interactions.

The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of α and β heterodimeric, transmembrane receptor molecules found in various combinations on nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell, 67, 1033 (1991); T. A. Springer, Cell, 76, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. 14, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, Ed.; Acad. Press, NY, 1996, p. 191).

VLA-4 ("very late antigen-4"; CD49d/CD29; or $\alpha 4\beta 1$) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, including dendritic cells and macrophage-like cells and is a key mediator of the cell-cell and cell-matrix interactions of of these cell types (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes." Ann. Rev. Immunol. 8, 365 (1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed in vivo on endothelial cells at sites of inflammation. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in Cellular and Molecular Mechanisms of Inflammation, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", Immunol. Today, 14, 506 (1993). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-Velag, NY, 1990.) A role for VLA-4/CS-1 interactions in inflammatory conditions has been proposed (see M. J. Elices, "The integrin $\alpha 4\beta 1$ (VLA-4) as a therapeutic target" in Cell Adhesion and Human Disease, Ciba Found. Symp., John Wiley & Sons, NY, 1995, p. 79).

$\alpha 4\beta 7$ (also referred to as LPAM-1 and $\alpha 4\beta_p$) is an integrin expressed on leukocytes and is a key mediator of leukocyte trafficking and homing in the gastrointestinal tract (see C. M. Parker et al., Proc. Natl. Acad. Sci. USA, 89, 1924 (1992)). The ligands for $\alpha 4\beta 7$ include mucosal addressing cell adhesion molecule-1 (MadCAM-1) and, upon activation of $\alpha 4\beta 7$, VCAM-1 and fibronectin (Fn). MadCAM-1 is a member of the Ig superfamily and is expressed in vivo on endothelial

cells of gut-associated mucosal tissues of the small and large intestine ("Peyer's Patches") and lactating mammary glands. (See M. J. Briskin et al., Nature, 363, 461 (1993); A. Hamann et al., J. Immunol., 152, 3282 (1994)). MadCAM-1 can be induced *in vitro* by proinflammatory stimuli (See E. E. Sikorski et al. J. Immunol., 151, 5239 (1993)). MadCAM-1 is selectively expressed at sites of lymphocyte extravasation and specifically binds to the integrin, $\alpha 4\beta 7$.

The $\alpha 9\beta 1$ integrin is found on airway smooth muscle cells, non-intestinal epithelial cells (see Palmer et al., J. Cell Biol., 123, 1289 (1993)), and neutrophils, and, less so, on hepatocytes and basal keratinocytes (see Yokosaki et al., J. Biol. Chem., 269,24144 (1994)). Neutrophils, in particular, are intimately involved in acute inflammatory repsonses. Attenuation of neutrophil involvement and/or activation would have the effect of lessening the inflammation. Thus, inhibition of $\alpha 9\beta 1$ binding to its respective ligands would be expected to have a positive effect in the treatment of acute inflammatory conditions.

Neutralizing anti-$\alpha 4$ antibodies or blocking peptides that inhibit the interaction between VLA-4 and/or $\alpha 4\beta 7$ and their ligands have proven efficacious both prophylactically and therapeutically in several animal models of disease, including i) experimental allergic encephalomyelitis, a model of neuronal demyelination resembling multiple sclerosis (for example, see T. Yednock et al., "Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha 4\beta 1$ integrin." Nature, 356, 63 (1993) and E. Keszthelyi et al., "Evidence for a prolonged role of $\alpha 4$ integrin throughout active experimental allergic encephalomyelitis." Neurology, 47, 1053 (1996)); ii) bronchial hyperresponsiveness in sheep and guinea pigs as models for the various phases of asthma (for example, see W. M. Abraham et al., "$\alpha 4$-Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. 93, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte recruitment and bronchial hyperresponsiveness in the gunea-pig." Eur. J. Pharmacol., 282, 243 (1995)); iii) adjuvant-induced arthritis in rats as a model of inflammatory arthritis (see C. Barbadillo et al., "Anti-VLA-4 mAb prevents adjuvant arthritis in Lewis rats." Arthr. Rheuma. (Suppl.), 36 95 (1993) and D. Seiffge, "Protective effects of monoclonal antibody to VLA-4 on leukocyte adhesion and course of disease in adjuvant arthritis in rats." J. Rheumatol., 23, 12 (1996)); iv) adoptive autoimmune diabetes in the NOD mouse (see J. L. Baron et al., "The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between $\alpha 4$-integrins and

vascular cell adhesion molecule-1.", J. Clin. Invest., 93, 1700 (1994), A. Jakubowski et al., "Vascular cell adhesion molecule-Ig fusion protein selectively targets activated α4-integrin receptors in vivo: Inhibition of autoimmune diabetes in an adoptive transfer model in nonobese diabetic mice." J. Immunol., 155, 938 (1995), and X. D. Yang et al., "Involvement of beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MadCAM-1) in the development of diabetes in nonobese diabetic mice", Diabetes, 46, 1542 (1997)); v) cardiac allograft survival in mice as a model of organ transplantation (see M. Isobe et al., "Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response to soluble antigens in mice.", Tranplant. Proc., 26, 867 (1994) and S. Molossi et al., "Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteripathy in rabbit cardiac allografts." J. Clin Invest., 95, 2601 (1995)); vi) spontaneous chronic colitis in cotton-top tamarins which resembles human ulcerative colitis, a form of inflammatory bowel disease (see D. K. Podolsky et al., "Attenuation of colitis in the Cotton-top tamarin by anti-α_4 integrin monoclonal antibody.", J. Clin. Invest., 92, 372 (1993)); vii) contact hypersensitivity models as a model for skin allergic reactions (see T. A. Ferguson and T. S. Kupper, "Antigen-independent processes in antigen-specific immunity.", J. Immunol., 150, 1172 (1993) and P. L. Chisholm et al., "Monoclonal antibodies to the integrin a-4 subunit inhibit the murine contact hypersensitivity response." Eur. J. Immunol., 23, 682 (1993)); viii) acute neurotoxic nephritis (see M. S. Mulligan et al., "Requirements for leukocyte adhesion molecules in nephrotoxic nephritis.", J. Clin. Invest., 91, 577 (1993)); ix) tumor metastasis (for examples, see M. Edward, "Integrins and other adhesion molecules involved in melanocytic tumor progression.", Curr. Opin. Oncol., 7, 185 (1995)); x) experimental autoimmune thyroiditis (see R. W. McMurray et al., "The role of α4 integrin and intercellular adhesion molecule-1 (ICAM-1) in murine experimental autoimmune thyroiditis." Autoimmunity, 23, 9 (1996); and xi) ischemic tissue damage following arterial occlusion in rats (see F. Squadrito et al., "Leukocyte integrin very late antigen-4/vascular cell adhesion molecule-1 adhesion pathway in splanchnic artery occlusion shock." Eur. J. Pharmacol., 318, 153 (1996; xii) inhibition of TH2 T-cell cytokine production including IL-4 and IL-5 by VLA-4 antibodies which would attenuate allergic responses (J.Clinical Investigation 100, 3083 (1997). The primary mechanism of action of such antibodies appears to be the inhibition of lymphocyte and monocyte interactions with CAMs associated with components of the

extracellular matrix, thereby limiting leukocyte migration to extravascular sites of injury or inflammation and/or limiting the priming and/or activation of leukocytes.

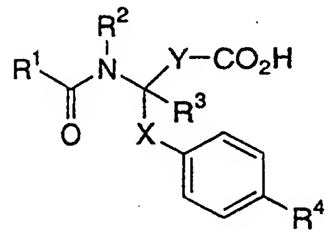
There is additional evidence supporting a possible role for VLA-4 interactions in other diseases, including rheumatoid arthritis; various melanomas, carcinomas, and sarcomas; inflammatory lung disorders; acute respiratory distress syndrome (ARDS); atherosclerotic plaque formation; restenosis; uveitis and circulatory shock (for examples, see A. A. Postigo et al., "The $\alpha_4\beta_1$/VCAM-1 adhesion pathway in physiology and disease.", Res. Immunol., 144, 723 (1994) and J.-X. Gao and A. C. Issekutz, "Expression of VCAM-1 and VLA-4 dependent T-lymphocyte adhesion to dermal fibroblasts stimulated with proinflammatory cytokines." Immunol. 89, 375 (1996)).

At present, there is a humanized monoclonal antibody (Antegren®, Athena Neurosciences/Elan) against VLA-4 in clinical development for the treatment of "flares" associated with multiple sclerosis and a humanized monoclonal antibody (ACT-1®/LDP-02 LeukoSite) against $\alpha_4\beta_7$ in clinical development for the treatment of inflammatory bowel disease. Several peptidyl antagonists of VLA-4 have been described (D. Y. Jackson et al., "Potent α4β1 peptide antagonists as potential anti-inflammatory agents", J. Med. Chem., 40, 3359 (1997); H. N. Shroff et al., "Small peptide inhibitors of α4β7 mediated MadCAM-1 adhesion to lymphocytes", Bioorg. Med. Chem. Lett., 6, 2495 (1996); US 5,510,332, WO99/10312, WO99/10313, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973). There are reports of nonpeptidyl inhibitors of the ligands for α_4-integrins (WO96/31206); A. J. Soures et al., Bioorg. Med. Chem. Lett., 8, 2297 (1998); K.-C. Lin et al., J. Med. Chem. 42, 920 (1999). There still remains a need for low molecular weight, specific inhibitors of VLA-4- and α4β7-dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention or suppression of various pathologies mediated by VLA-4, α4β7, and α9β1 binding and cell adhesion and activation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for the prevention or treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in

a mammal which comprises administering to said mamal an effective amount of a compound of Formula I:



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or a pharmaceutically acceptable salt thereof wherein:

R^1 is 1) aryl,
2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^2 is 1) hydrogen,
2) C_{1-10}alkyl,
3) C_{2-10}alkenyl,
4) C_{2-10}alkynyl,
5) C_{3-7}cycloalkyl,
6) aryl,
7) heteroaryl,

wherein alkyl, alkenyl, alkynyl are optionally substituted with one to four substituents independently selected from R^a; cycloalkyl, aryl, and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^3 is 1) hydrogen,
2) C_{1-10}alkyl,
3) C_{2-10}alkenyl,
4) C_{2-10}alkynyl,
5) aryl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a, and aryl is optionally substituted with one to four substituents independently selected from R^a,

R^4 is
1) hydrogen,
2) C_{1-10}alkyl,
3) hydroxy,
4) C_{1-10}alkoxy,
5) Z-R^1,
6) C_{2-10}alkenyl,
7) C_{2-10}alkynyl,
8) -$O(CR^fR^g)_nNR^dR^e$,
9) -$OC(O)R^d$,
10) -$OC(O)NR^dR^e$,
11) -$S(O)_mR^d$,
12) -$S(O)_2OR^d$,
13) -$S(O)_mNR^dR^e$,
14) -$C(O)R^d$,
15) -CO_2R^d,
16) -$C(O)NR^dR^e$,

wherein alkyl, alkenyl, alkynyl and alkoxy are optionally substituted with one to four substituents selected from R^a,

R^a is
1) aryl,
2) -OR^d,
3) -NO_2,
4) halogen
5) -$S(O)_mR^d$,
6) -SR^d,
7) -$S(O)_2OR^d$,
8) -$S(O)_mNR^dR^e$,
9) -NR^dR^e,
10) -$O(CR^fR^g)_nNR^dR^e$,
11) -$C(O)R^d$,
12) -CO_2R^d,

13) $-CO_2(CR^fR^g)_nCONR^dR^e$,

14) $-OC(O)R^d$,

15) -CN,

16) $-C(O)NR^dR^e$,

17) $-NR^dC(O)R^e$,

18) $-OC(O)NR^dR^e$,

19) $-NR^dC(O)OR^e$,

20) $-NR^dC(O)NR^dR^e$,

21) $-CR^d(N-OR^e)$,

22) CF_3,

23) $-OCF_3$, or

24) heteroaryl;

R^b is

1) a group selected from R^a,

2) C_{1-10} alkyl,

3) C_{2-10} alkenyl,

4) C_{2-10} alkynyl,

5) aryl C_{1-10}alkyl,

6) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

R^c is

1) halogen,

2) amino,

3) carboxy,

4) C_{1-4}alkyl,

5) C_{1-4}alkoxy,

6) aryl,

7) aryl C_{1-4}alkyl,

8) hydroxy,

9) CF_3, or

10) aryloxy;

R^d and R^e are independently selected from hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, Cy and Cy C_{1-10}alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from R^c; or

R^d and R^e together with the nitrogen atom to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C_{1-10}alkyl, Cy and Cy-C_{1-10}alkyl; or

R^f and R^g together with the carbon atom to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from N, O and S;

Cy is independently selected from cycloalkyl, heterocyclyl, aryl, or heteroaryl;

m is an integer from 1 to 2;

n is an integer from 1 to 10;

X and Y are independently a bond or C_{1-2}alkylene;

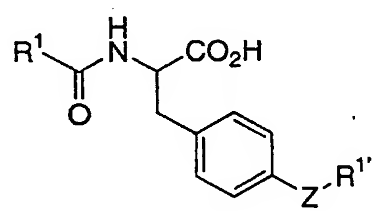
Z is
1) a bond,
2) O,
3) $S(O)_m$,
4) C_{1-10}alkylene,

or a pharmaceutically acceptable salt thereof.

In one embodiment said disease or disorder is selected from asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, and inflammatory bowel disease.

In another aspect the present invention provides a method for preventing the action of VLA-4 in a mammal which comprises administering to said mammal a thereapeutically effective amount of a compound of formula I.

In another aspect the present invention provides novel compounds of the formula Ia:



Ia

wherein R^1 and $R^{1'}$ are independently selected from
1) aryl,
2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^b is independently selected from:

1) aryl,
2) $-OR^d$,
3) $-NO_2$,
4) halogen
5) $-S(O)_mR^d$,
6) $-SR^d$,
7) $-S(O)_2OR^d$,
8) $-S(O)_mNR^dR^e$,
9) $-NR^dR^e$,
10) $-O(CR^fR^g)_nNR^dR^e$,
11) $-C(O)R^d$,
12) $-CO_2R^d$,
13) $-CO_2(CR^fR^g)_nCONR^dR^e$,
14) $-OC(O)R^d$,
15) -CN,
16) $-C(O)NR^dR^e$,
17) $-NR^dC(O)R^e$,
18) $-OC(O)NR^dR^e$,
19) $-NR^dC(O)OR^e$,
20) $-NR^dC(O)NR^dR^e$,
21) $-CR^d(N-OR^e)$,
22) CF_3,
23) $-OCF_3$,
24) heteroaryl
25) C_{1-10} alkyl,
26) C_{2-10} alkenyl,
27) C_{2-10} alkynyl,
28) aryl C_{1-10}alkyl,
29) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

R^c is
1) halogen,
2) amino,
3) carboxy,
4) C_{1-4}alkyl,
5) C_{1-4}alkoxy,
6) aryl,
7) aryl C_{1-4}alkyl,
8) hydroxy,
9) CF_3, or
10) aryloxy;

R^d and R^e are independently selected from hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, Cy and Cy C_{1-10}alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from R^c; or

R^d and R^e together with the nitrogen atom to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C_{1-10}alkyl, Cy and Cy-C_{1-10}alkyl; or

R^f and R^g together with the carbon atom to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from N, O and S;

Cy is independently selected from cycloalkyl, heterocyclyl, aryl, or heteroaryl;

Z is
1) a bond,
2) O,
3) $S(O)_m$,
4) C_{1-10}alkylene,

m is an integer from 1 to 2;

n is an integer from 1 to 10;

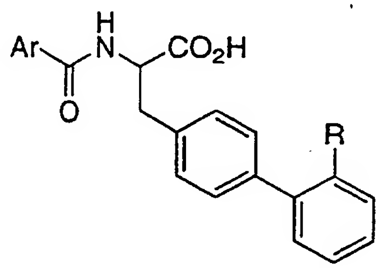
or a pharmaceutically acceptable salt thereof.

In one embodiment of compounds of formula Ia, R^1 is phenyl or a heteroaryl selected from the group consisting of furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyrimidinyl, and pyridyl, each of the phenyl and heteroaryl is optionally substituted with 1 or 2 groups independently selected from OR^d, halogen, C_{1-3}alkyl optionally substituted with a group selected from R^c, $S(O)_mR^d$ and SR^d.

Examples of specific R^1 include phenyl, furyl, thienyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, methoxyphenyl, hydroxypyridyl, methylthienyl, (aminomethyl)phenyl, biphenyl, (methylsulfonyl)phenyl, (phenylthio)phenyl, 2,6-dichloropyridyl, (phenylsulfonyl)phenyl, and 2-bromo-6-methylphenyl.

In another embodiment of compounds of formula Ia, Z is a bond and $R^{1'}$ is phenyl bearing a substituent at the atom adjacent to the atom connected to Z.

Representative compounds of formula Ia are as follows:



Ar	R
Ph	CN
Ph	OCH_3
2-furyl	CN
3-furyl	CN
2-OCH_3-Ph	CN
3-OCH_3-Ph	CN
4-OCH_3-Ph	CN
2-pyridyl	CN
2-pyridyl	OCH_3
6-OH-2-pyridyl	CN
3-CH_3-2-thienyl	CN
4-NH_2CH_2-Ph	CN
2-Ph-Ph	CN
2-Ph-Ph	OCH_3
2-Br-6-CH_3-Ph	OCH_3
2-pyrrolyl	OCH_3
2-CH_3SO_2-Ph	OCH_3
2-PhS-Ph	OCH_3

2-$PhSO_2$-Ph	OCH_3

In the application, unless otherwise specified, the following terms are as defined.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 10 carbon atoms. The term also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. The term also includes aryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like.

"Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Heterocyclyl" means mono- or bicyclic saturated rings containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. The term also includes monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, tetrahydroisoquinolinyl, dihydroindolyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted-(1H,3H)-pyrimidine-2,4-diones (N-substituted uracils).

"Halogen" includes fluorine, chlorine, bromine and iodine.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The ability of the compounds of Formula I to antagonize the actions of VLA-4 and/or α4β7 integrin makes them useful for preventing or reversing the symptoms, disorders or diseases induced by the binding of VLA-4 and or α4β7 to their various respective ligands. Thus, these antagonists will inhibit cell adhesion processes including cell activation, migration, proliferation and differentiation. Accordingly, another aspect of the present invention provides a method for the treatment (including prevention, alleviation, amelioration or suppression) of diseases or disorders or symptoms mediated by VLA-4 and/or α4β7 binding and cell adhesion

and activation, which comprises administering to a mammal an effective amount of a compound of Formula I. Such diseases, disorders, conditions or symptoms are for example (1) multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) allergic conjunctivitis, (5) inflammatory lung diseases, (6) rheumatoid arthritis, (7) septic arthritis, (8) type I diabetes, (9) organ transplantation rejection, (10) restenosis, (11) autologous bone marrow transplantation, (12) inflammatory sequelae of viral infections, (13) myocarditis, (14) inflammatory bowel disease including ulcerative colitis and Crohn's disease, (15) certain types of toxic and immune-based nephritis, (16) contact dermal hypersensitivity, (17) psoriasis, (18) tumor metastasis, and (19) atherosclerosis.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders

which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of

bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

Water for injection to a total volume of 1 mL

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula I	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) other VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973 and WO96/31206; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine,

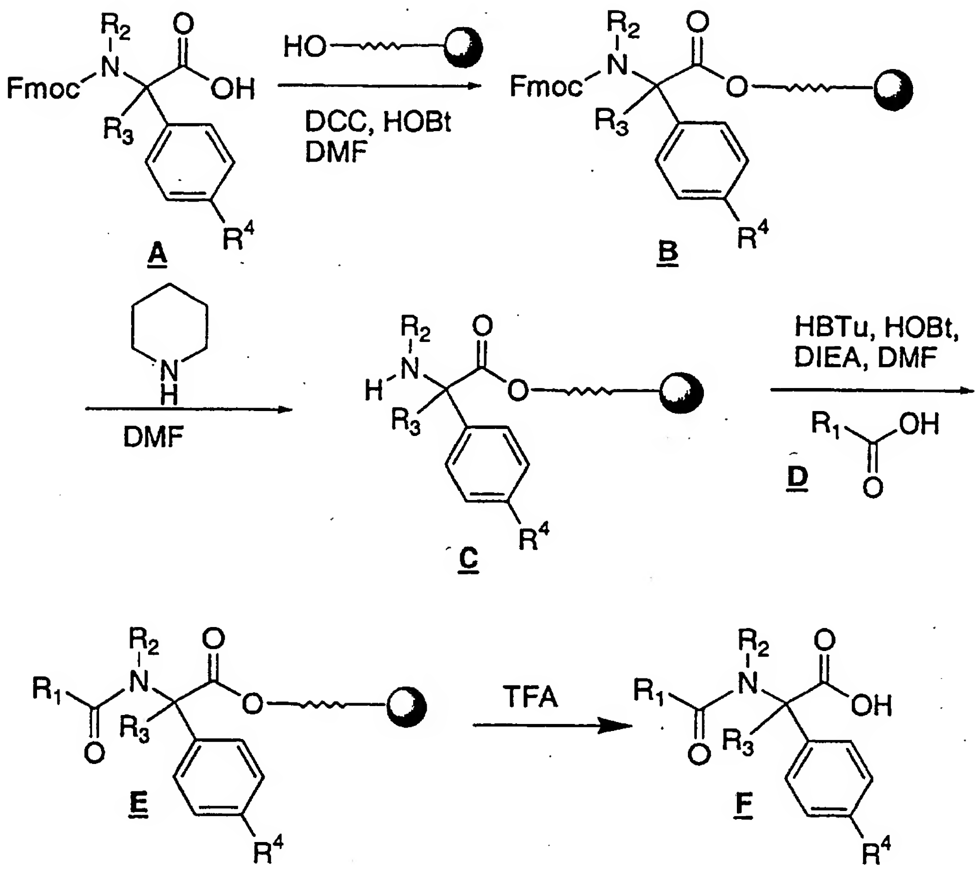
descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as b2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors, especially CCR-1, CCR-2, and CCR-3; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), a-glucosidase inhibitors (acarbose) and glitazones (troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like); (l) preparations of interferon beta (interferon beta-1a, interferon beta-1b); (m) anticholinergic agents such as muscarinic antagonists (ipratropium bromide); (n) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents.

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of

the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Compounds of the present invention may be prepared by procedures illustrated in the accompanying schemes. In the first method (Scheme 1), a resin-based synthetic strategy is outlined where the resin employed is represented by the ball (❍). An N-Fmoc-protected amino acid derivative A (Fmoc = fluorenylmethoxycarbonyl) is loaded on to the appropriate hydroxyl-containing resin (the choice of resin being dependent on type of linker used; in this case Wang resin was utilized) using dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) in a solvent such as methylene chloride and tetrahydrofuran (THF) or dimethylformamide (DMF) to give B. The Fmoc protecting group is removed with piperidine in DMF to yield free amine C. A carboxyxlic acid **D** is then coupled to the amine using a reagent such as 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTu) in the presence of HOBt and diisopropyl ethyl amine (DIEA) or any of the other well known amide coupling reagents under appropriate conditions: EDC, DCC or BOP (benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate) to give **E**. The final product is removed from the resin with strong acid (in this instance, trifluoroacetic acid (TFA in the presence of 5% water) to yield compounds of the present invention F.

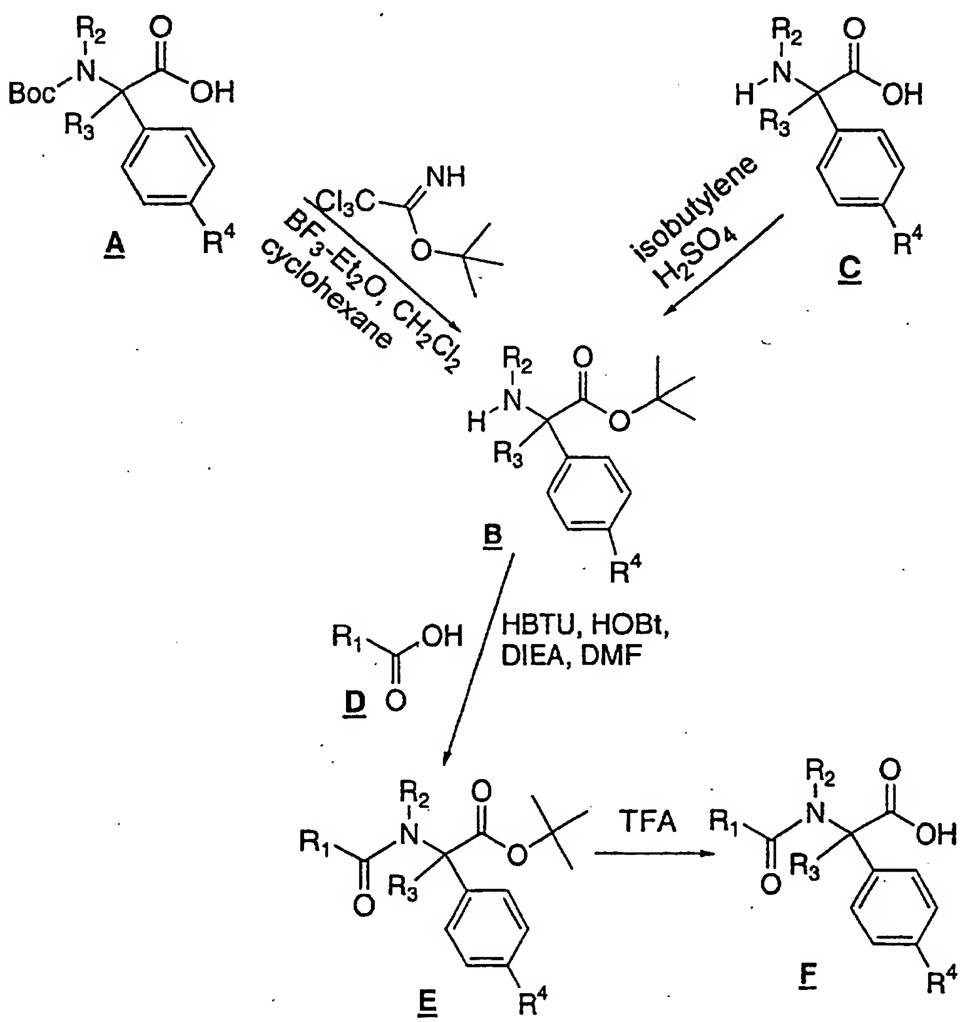
Scheme 1.



In the second method (Scheme 2), standard solution phase synthetic methodology is outlined. Many amino acids are commercially available as the t-butyl or methyl esters and may be used directly in the synthesis outlined below. Amino acid t-butyl esters B may be prepared from amino acids C directly by treament with isobutylene and sulfuric acid in diglyme or dioxane. Alternatively, N-Boc-protected amino acid derivative A (Boc = tert-butyloxycarbonyl) is treated with tert-butyl 2,2,2-trichloroacetimidate in the presence of boron trifluoride etherate (BF_3-Et_2O) followed by treatment with strong acid (hydrochloric acid, HCl in ethyl acetate or sulfuric acid in t-butyl acetate) to remove the t-BOC group to yield tert-butyl ester B which is subsequently coupled to carboxylic acid D in the presence of EDC, HBTu, HOBt, and diisopropylethylamine (DIEA) in methylene chloride to yield amide E. The ester is

then hydrolysed (in the case of t-butyl ester with 50% TFA in methylene chloride and for the methyl ester by treatment with 1N sodium hydroxide solution in methanol or dioxane) to provide compounds of the present invention **F**.

Scheme 2

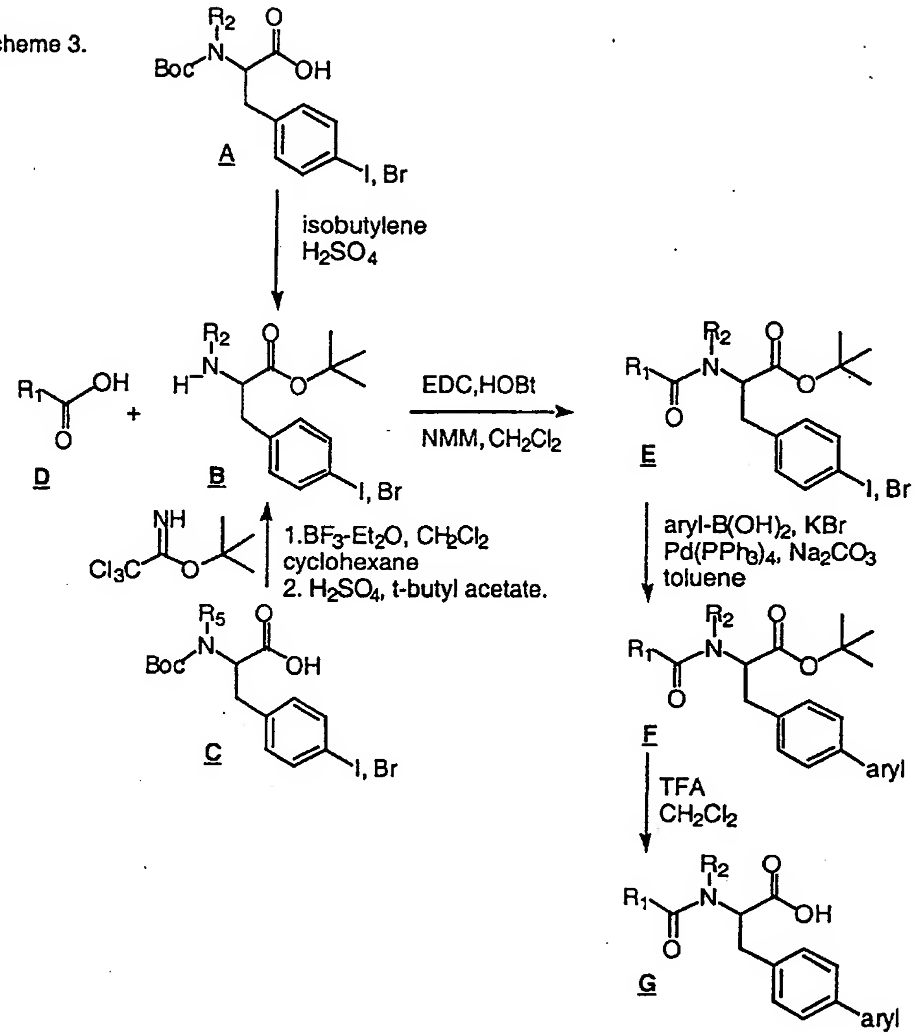


Note: methyl esters may be used in place of t-butyl esters. E to F by treament with 1N NaOH

In a third method (Scheme 3), a late stage intermediate aryl bromide or iodide is coupled to an appropriately substituted aryl or heteroaryl boronic acid to give

a subset of compounds of the present invention (R^3 = biaryl-substituted alkyl, R^2 = hydrogen). For example, 4-iodo or 4-bromo phenylalanine A is converted to the t-butyl ester **B** by treatment with isobutylene and sulfuric acid. Alternatively N-Boc-4-iodo- or 4-bromo-phenylalanine C is reacted with *tert*-butyl 2,2,2-trichloroacetimidate in the presence of boron trifluoride etherate in methylene chloride-cyclohexane followed by treatment with strong acid (HCl in ethyl acetate or sulfuric acid in t-butyl acetate) to remove the t-BOC group to yield tert-butyl ester B which is subsequently coupled with C in the presence of EDC, HOBt and NMM to yield 4-iodo- or 4-bromo-phenylalanine dipeptide E. Substituted aryl or heteroaryl boronic acids are coupled to E in the presence of a palladium(0) reagent, such as tetrakis(triphenylphosphine)-palladium under Suzuki conditions (N. Miyaura *et al.*, *Synth. Commun.*, **1981**, *11*, 513-519) to yield G. The tert-butyl ester is then removed by treatment with strong acid (TFA) to yield the desired product F. If the aryl or heteroaryl boronic acid is not commercially available, but the corresponding bromide or iodide is, then the bromide or iodide can be converted into the desired boronic acid by treatment with an alkyllithium reagent in tetrahydrofuran at low temperature followed by addition of trimethyl or triisopropyl borate. Hydrolysis to the boronic acid can be effected by treatment of the intermediate with aqueous base and then acid.

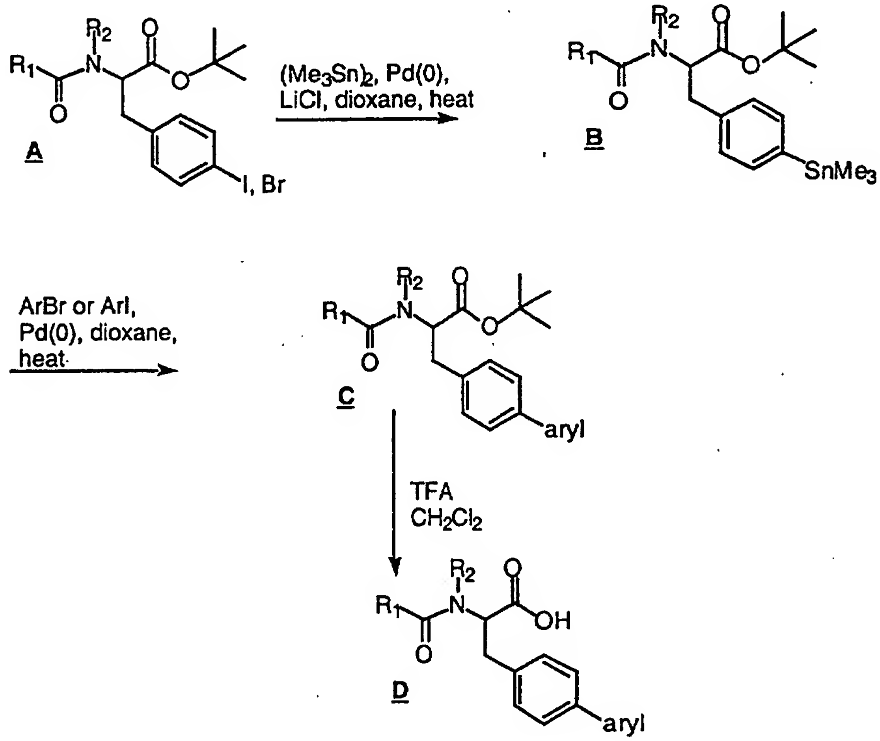
Scheme 3.



Alternatively, the aryl coupling reaction may be performed by application of Stille-type carbon-carbon bond forming conditions (Scheme 4). (A.M. Echavarren and J.K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486). The aryl bromide or iodide intermediate **A** is converted into its trialkyltin derivative **B** using hexamethylditin in the presence of a palladium(0) catalyst and lithium chloride and then reacted with an appropriately substituted aryl or heteroaryl bromide, iodide, or triflate in the presence of a palladium reagent, such as tetrakis(triphenylphosphine)-palladium(0) or tris(dibenzylideneacetone)dipalladium(0), in a suitable solvent, such as toluene, dioxane, DMF, or 1-methyl-2-pyrrolidinone, to give intermediate **C**. The

tert-butyl ester is then removed by treatment with strong acid (TFA) to yield the desired product **D**. Biphenyl amino acids suitable for attachment to resin (**D** where R_1 is fluorenylmethyloxy) may be prepared by this route as well. Superior coupling conversions and rates may be elicited by application of the method of Farina (J. Org. Chem. 5434 1993)

Scheme 4.



The following examples are provided to illustrate the invention and are not to be construed as limiting the scope of the invention in any manner.

PREPARATIVE EXAMPLE 1

N-FMOC-(S)-4-(2'-cyanophenyl)phenylalanine.

Step A. N-FMOC-(L)-4-iodophenylalanine, t-butyl ester.

To a solution of 15g (51 mmol) of (L)-4-iodophenylalanine in 100 ml of diglyme and 15 ml of concentrated H_2SO_4 was added 30 ml of condensed

isobutylene. The vessel was agitated overnight and the crude product was diluted with 100 ml of ethyl acetate. The solution was added to excess sodium hydroxide solution while maintaining the temperature below 30°C. A white precipitate formed which dissolved upon addition of sodium hydroxide solution. The resulting mixture was filtered and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated in vacuo to give a solution of the product in diglyme. The solution was diluted with 200 ml of ether and was treated with excess 1N HCl in ether with rapid stirring. The resulting precipitate was collected and dried in vacuo after washing with ether. A white solid (9.01 g) was collected of 4-iodophenylalanine t-butyl ester hydrochloride. To a suspension of 5.1 g (13.3 mmol) of the amine hydrochloride in 30 ml of methylene chloride was added 3.6 g (27 mmol) of diisopropyl ethyl amine followed by 3.43 g (0.013 g) of FMOCCl. The solution was stirred overnight at room temperature, washed with 1N HCl solution (3 x 50 ml), water (1 x 50 ml), saturated sodium carbonate solution (2 x 50 ml) and brine (1 x 50 ml). The solution was dried over $MgSO_4$, filtered and concentrated in vacuo to give 6.43 g of N-FMOC-(L)-4-iodophenylalanine, t-butyl ester as a white foam.
300 MHz ^1H NMR ($CDCl_3$): d 1.44 (s, 9 H); 3.05 (d, 2H);4.20 - 4.60 (m, 4 H); 5.30 (m, 1H); 6.90 (d, 2H), 7.30 - 7.80 (m, 12H).

Step B. N-FMOC-(L)-4-trimethylstannylphenylalanine, t-butyl ester.

In a dry 250 ml round bottom flask was added 6.20g (10.5 mmol) of the product of Step A, 0.48 g (115 mmol) LiCl and 0.6 g (0.52 mmol) of palladium tetrakistriphenylphosphine followed by 50 ml of dry dioxane. The mixture was stirred for 5 minutes. 5.2 g (15.8 mmol) of hexamethylditin was added and the reaction mixture was degassed and then heated at 90°C. The reaction mixture gave a black suspension after 15 minutes. Completion of the conversion was determined by TLC (10% EtOAc/hexanes; sm r.f .= 0.3, product r.f. = 0.4). The mixture was diluted with 100 ml of hexanes and stirred to give a precipitate. The suspension was filtered through celite and concentrated in vacuo to give a gum. The residue was purified by flash chromatography over silica gel eluting with 10% EtOAc/hexanes to give 5.02 g of the stannane (77% yield).
300 MHz ^1H NMR ($CDCl_3$): d 0.30 (s, 9 H); 1.45 (s, 9H); 3.20 (d, 2H), 4.20-4.60 (m, 4H); 5.29 (d, 1H); 7.12 (d, 2H); 7.22-7.45 (m, 6H); 7.59 (d, 2H), 7.75 (d, 2H).

Step C. N-FMOC-(S)-4-(2'-cyanophenyl)phenylalanine, t-butyl ester.

In a clean, dry round bottom flask fitted with a reflux condenser vented through a three way valve attached to a vacuum source and nitrogen gas was added 1.56 g (6.8 mmol) of 2-iodobenzonitrile, 0.117 (0.12 mmol) of tris(dibenzylidine-acetone)dipalladium (0), 0.8 g (19 mmol) of LiCl and 0.15 g (0.5 mmol) of triphenylarsine followed by 30 ml of N-methylpyrrolidinone (NMP). The mixture was degassed and stirred for 10 minutes at which time most of the catalyst mixture had dissolved. 3.9 g (6.21 mmol) of the product of Step B was added in 10 ml of NMP and the reaction was heated to 80oC for 90 minutes. TLC (10% EtOAc/hexanes) indicated complete consumption of stannane (rf=0.4) and formation of the desired product (rf=0.1). The solution was cooled to room temperature and diluted with 50 ml of EtOAc. The solution was stirred with 20 ml of saturated KF for 20 minutes. The mixture was diluted with 200 ml of EtOAc and washed with water (6 x 75 ml), brine (1 x 50 ml) and was dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo and the residue was purified by Biotage Flash chromatography over silica gel eluting with 20% EtOAc/hexanes to give 1.91 g (54% yield) of the title compound.

300 MHz ^1H NMR ($CDCl_3$): δ 1.45 (s, 9H); 3.19 (d, 2H); 4.20-4.68 (m, 4H); 5.40 (d, 1H); 7.25-7.55 (m, 12H); 7.65 (m, 2H), 7.80 (d, 2H).

Step D. N-FMOC-(S)-4-(2'-cyanophenyl)phenylalanine.

2.4 g of the product of Step C was treated with 50 ml of a mixture of 50% trifluoroacetic acid in methylene chloride. The reaction mixture was concentrated in vacuo. The residue was azeotropically dried by concentration from toluene to give the desired product as a foam.

300 MHz ^1H NMR (CD_3OD): d 3.02 (dd, 1H); 3.30 (dd, 1H); 4.05-4.35 (m, 3H); 4.52 (m, 1H); 7.10-7.50 (m, 12H); 7.60 (m, 2H), 7.78 (d, 2H).

PREPARATIVE EXAMPLE 2

N-(FMOC)-(S)-2'-methoxy-biphenylalanine

Step A. N-(Butyloxycarbonyl)-(S)-4-iodo-phenylalanine, t-butyl ester.

To a suspension of 7.5 g (0.019 m) of 4-iodophenylalanine t-butyl ester (Example 1, Step A prior to treatment with HCl) in 100 ml of dichloromethane was

added 2.52 g 0.019 m of diisopropyl ethyl amine followed by 4.14 g of ditertbutyldicarbonate. The reaction mixture was stirred over night at room temperature, washed with 1N HCl (2 x 25 ml), water (2 x 25 ml), saturated $NaHCO_3$ (1 x 25 ml), brine (1 x 25 ml) and was dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo to to give the desired product as a gum 8.8 g (100% yield). 300 MHz ^1H NMR ($CDCl_3$): 1.39 (s, 18H); 2.98 (AB, 2H); 4.4 (dd, 2H); 5.0 bd, 1H); 6.92 (d, 2H); 7.62 (d, 2H).

Step B. N-(Butyloxycarbonyl)-(S)-4-(2'-methoxyphenyl)phenylalanine, t-butyl ester.

7.97 g (0.018 m) of the product of Step A was dissolved in 160 ml of 2:1 toluene:ethanol. To this solution was added 2.99 g (0.0198 m) 2-methoxyphenyl-boronic acid, 0.69 g of tetrakistriphenylphosphine palladium (0) and 22.7 ml (0.45 m) of 2.0 M sodium carbonate in water. The reaction mixture was degassed three times and then heated at 90°O for 90 minutes at which time the reaction mixture was black. The mixture was diluted with 300 ml of ethyl acetate and was washed with water (3 x 150 ml) and brine (2 x 100 ml) and was dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 10% EtOAc/hexanes to give 6.89 g (88% yield) of the desired product as a white solid. 300 MHz ^1H NMR ($CDCl_3$): 1.45 (s, 18H); 3.10 (d, 2H); 3.80 (s, 3H); 4.5 (dd, 2H); 5.1 bd, 1H); 7.0 (m, 2H); 7.22 (d, 2H); 7.30 (d, 2H); 7.49 (d, 2H); 7.62 (d, 2H).

Step C. N-(FMOC)-(S)-4-(2'-methoxyphenyl)phenylalanine.

To a solution of 4.85 g (0.0113 m) of the product of Step B in 100 ml of t-butyl acetate was added 5.53 g (0.056 m) of concentrated sulfuric acid. The solution was stirred at room temperature for 2 hours and then carefully neutralized by addition of saturated aqueous $NaHCO_3$ solution. The solution was washed with $NaHCO_3$ solution, dried over $NaSO_4$, filtered and concentrated in vacuo. To a solution of 4.42 g of amine in 150 ml of methylene chloride was added at 0°C 1.74 g (13.5 mmol) of diisopropylethyl amine followed by 3.48 g (13.5 mmol) of FMOCCl. The solution was stirred for 2 hours and washed with 1N HCl (3 x 50 ml), saturated $NaHCO_3$ solution (2 x 50 ml) and brine (1 x 50 ml). The mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica

gel eluting with a gradient of 10-25% EtOAc/hexanes to give 7.10 g (88% yield) of the desired product as a glass. The material was dissolved in 125 ml of 50% trifluoracetic acid/methylene chloride and stirred at room temperature for 2.5 hours. The solution was concentrated in vacuo and the residue was redissolved in toluene and concentrated in vacuo to give 7.01 g of the desired product. 96% pure by HPLC (254 nm). 300 MHz ^{1}H NMR ($CDCl_3$): 3.20 (m, 2H); 3.76 (s, 3H); 4.21 (t, 1H); 4.41 (m, 4H); 4.76 (dd, 1H); 5.32 (d, 1H); 6.8-7.8 (m, 16H).

PREPARATIVE EXAMPLE 3

N-(FMOC)- (L)-4-(1-pyrrolidino-carbonyloxy)phenylalanine.

Step A. <u>N-(Butyloxycarbonyl)- (L)-tyrosine-t-butyl ester.</u>

To a solution of 9.82 g (0.041 m) of tyrosine t-butyl ester in 150 ml of methylene chloride and 20 ml of DMF was added 5.2 g (0.04 m) of triethyl amine followed by 9.03 g (0.04 m) of ditertbutyldicarbonate. The reaction mixture was stirred for 2 hours at room temperature and was then washed with 1 N HCl (3 x 50 ml), $NaHCO_3$ solution (1 x 50 ml) and brine (1 x 50 ml) and was dried over $MgSO_4$. The mixture was filtered and concentrated in vacuo to give 13.59 g (98% yield) of a white solid.). 300 MHz ^{1}H NMR ($CDCl_3$):1.42 (s, 18H); 2.95 (d, 2H); 4.39 (dd, 1H); 5.01 (d, 1H); 6.15 (s, 1H); 6.70 (d, 2H); 7.00 d, 2H).

Step B. N-(Butyloxycarbonyl)- (L)-4-(1-pyrrolidino-carbonyloxy)phenylalanine t-butyl ester.

To a solution A N_2 of 8.18 g (0.024 m) of the product of Step A in a clean, dry flask dissolved in 100 ml of THF was added at 0°C 25.5 ml (0.025 m) of a 1M solution of sodium hexamethyldisilazide in THF. The solution was stirred for 20 minutes. A solution of 3.2 g (0.024 m) of pyrrolidine carbamoyl chloride in 10 ml of THF was added. The reaction mixture was allowed to warm to room temperature and was stirred for 48 hours. The solution was diluted with 100 ml of ethyl acetate and was washed with 1N HCl (3 x 75 ml), saturated $NaHCO_3$ (1 x 75 ml), 1N NaOH (2 x 75 ml) and brine (1 x 75 ml) and was dried over $MgSO_4$. . The mixture was filtered and concentrated in vacuo and the residue was recrystalized from ethyl acetate/hexanes to give 8.6 g of a white solid. 300 MHz ^{1}H NMR ($CDCl_3$): 1.40 (s,

9H); 1.41 (s, 9H); 1.92 (m, 4H); 3.02 (d, 2H); 3.45 (t, 2H); 3.55 (t, 2H); 4.42 (dd, 1H); 4.99 (d, 1H); 7.05 (d, 2H); 7.15 (d, 2H).

Step C. N-(FMOC)- (L)-4-(1-pyrrolidino-carbonyloxy)phenylalanine.

The method of Example 2 Step C was applied to 8.1 g (0.018 m) of the product of Step A to give 6.27 g of the desired product as a foam. 71% overall yield. 300 MHz ^{1}H NMR ($CDCl_3$): 1.97 (bs, 4H); 3.12 (bd, 2H); 3.4-3.6 (2 bm, 4H); 4.20 (m, 1H); 4.30-4.50 (m, 2H); 4.69 m, 1H); 5.59 (t, 1H); 7.00-7.42 (m, 8H); 7.55 (bm, 2H); 7.77 (d. 2H).

PREPARATIVE EXAMPLE 4

(S)-4-(2'-methoxyphenyl)phenylalanine, t-butyl ester hydrochloride.

To a solution of 4.85 g (0.0113 m) of the product of Example 2, Step B in 100 ml of t-butyl acetate was added 5.53 g (0.056 m) of concentrated sulfuric acid. The solution was stirred at room temperature for 2 hours and then carefully neutralised by addition of saturated aqueous $NaHCO_3$ solution. The solution was washed with $NaHCO_3$ solution, dried over $NaSO_4$. filtered and concentrated in vacuo. The residue was dissolved in 50 ml of ether and treated with anhydrous HCl gas with stirring to give a white precipitate. The solid was collected by filtration, washed with ether and dried in vacuo to give the desired product. 300 MHz ^{1}H NMR (CD_3OD): 1.45 (s, 9H); 3.20 (d, 2H); 3.79 (s, 3H); 4.21 (t, 1H); 7.03 (m, 2H); 7.28 (m, 2H); 7.31 (d, 2H); 7.50 (d, 2H).

PREPARATIVE EXAMPLE 5

General procedure for the solid-phase synthesis of compounds of Formula 1.

Described below is the method used for preparing N-FMOC-(S)-4-(2'-cyanophenyl)phenylalanine resin. Application of the identical method to the amino acids described in Examples 2 and 3 provided the appropriate resins for preparation of the examples prepared via solid phase chemistry. Some commercially available N-FMOC-amino acid resins were also utilized. All reactions were carried out in polyethylene syringes fitted with frits (Applied Separations) and capped with adaptors (Varian) and teflon stopcocks (Jones Chromatography). Agitation of the vessels was performed by rotation on a tube rotator.

Step A. Loading of N-FMOC-(S)-4-(2'-cyanophenyl)phenylalanine onto resin.

5.0 g (4.75 mmol based on 0.95 mmol/g capacity) of Wang resin (Bachem) was suspended in 60 ml of 50% THF/CH_2Cl_2 (sufficient to ensure semi-fluid state) and treated with 4.64 g (9.5 mmol) of N-FMOC-(L)-2'-cyano-biphenyl-alanine, 1.81 g (9.5 mmol) of EDC and 0.63 g (4.7 mmol) of DMAP. The mixture was agitated for 2.5 hours and filtered through the integral frit. The resin was washed twice with 50% THF/CH_2Cl_2 (50 ml) and the reaction was repeated as above. The mixture was filtered though the integral frit and washed: THF/CH_2Cl_2 (3 x 50 ml), CH_2Cl_2 (2 x 50 ml), MeOH (2 x 50 ml), CH_2Cl_2 (50 ml), MeOH (50 ml), CH_2Cl_2 (2 x 50 ml) and ether (2 x 50 ml). The resin was dried in vacuo to give 7.20 g of the desired product.

Loading was evaluated by treating 50 mg of the resin in a 2 ml polyethylene syringe with 95% TFA/H_2O (3 x 2 ml for 10 minutes). The combined filtrates were concentrated in vacuo and the residue was weighed and analysed by HPLC, NMR. The loading of the resin from Step A was 0.78 mmol/g and the recovered amino acid was >90% pure by HPLC (210 nM).

Step B. Deprotection of the FMOC group.

30 mg (0.028 mmol based on 0.95 mmol/g loading) of the resin from Step A was placed in a 2 ml polyethylene frit fitted syringe. The syringe outlet was capped by a teflon stopcock. The resin was treated with 2ml (3 x 10 min) of 20% piperidine in DMF. Following the final treatment the resin was washed with DMF (3 x 2 ml).

Step C. Coupling to carboxylic acids.

The resin from Step B (in the same reaction vessel) was treated with a solution made up in 1.5 ml of DMF of: 0.112 mmol of the carboxylic acid, 0.112 mmol of HBTU, 0.112 mmol of HOBt.H_2O and 0.14 mmol of diisopropylethylamine. The vessel was capped with an adaptor and teflon stopcock and rotated over night. The reaction mixture was filtered and the resin was washed with DMF (3 x 2 ml) followed by CH_2Cl_2 (2 x 2 ml). A 1 mg aliquot of the resin was submitted to the Kaiser test to confirm that all primary amine had been acylated. If the conversion was complete the resin was washed: : DMF (3 x 2 ml), CH_2Cl_2 (2 x 2 ml), MeOH (2 x 2 ml), CH_2Cl_2 (2 ml), MeOH (2 ml), CH_2Cl_2 (3 x 2 ml). If the resin was not completely acylated the reaction was repeated.

Step D. Cleavage of the product from the resin.

The resin (in the original vessel) was treated with 95% TFA/H_2O (3 x 1.5 ml) and the resulting filtrates were collected in a previously tared 13mm x 100mm test tube. The filtrate was concentrated in vacuo in a rotory concentrator. The residue was dissolved in approximatly 3 ml of 30% CH_3CN/H_2O and aliquots were removed for HPLC and MS analysis. The solution was then lyophilized to provide the desired product. Criteria for assay included >80 % purity by HPLC and structure was confirmed by mass spectrum.

The following amides were prepared by the procedures described in PREPARATIVE EXAMPLE 5 using the appropriate carboxylic acid and amino acid derivatives:

Ex. No.	Name	Mass Spectrum*
1	N-(benzoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	371
2	N-(benzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine	376
3	N-(2-furoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	361
4	N-(3-furoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	361
5	N-(2-anisoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	401
6	N-(3-anisoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	401
7	N-(4-anisoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	401
8	N-(2-picolinoyl)-(L)-4-(2'-cyanophenyl)phenylalanine	386
9	N-(2-picolinoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine	377
10	N-(6-hydroxy-2-picolinoyl)-(L)-4-(2'-cyanophenyl)-phenylalanine	388
11	N-(3-methyl-2-thienoyl)-(L)-4-(2'-cyanophenyl)-phenylalanine	391
12	N-(4-aminomethyl-benzoyl)-(L)-4-(2'-cyanophenyl)-phenylalanine	400
13	N-(3-methoxy-benzoyl)-3(R,S)-amino-3-phenyl-propionic acid	285

14	N-(2-methoxy-benzoyl)-3(R,S)-amino-3-phenyl-propionic acid	300
15	N-(4-methoxy-benzoyl)-3(R,S)-amino-3-phenyl-propionic acid	300

Mass spectrum m/e (M^+ or $M+1(H^+)^+$ or $M+18\ (NH_4^+)^+$)

EXAMPLE 16

N-(2-Phenylbenzoyl)-(L)-4-(2'-cyanophenyL)phenylalanine.

Step A. N-(2-Phenylbenzoyl)-(L)-4-(2'-cyanophenyL)phenylalanine, methyl ester.

To a solution of 2-phenylbenzoic acid (Aldrich, 50 mg, 0.25 mmol) and (L)-4-(2'-cyanophenyl)phenylalanine, methyl ester (76 mg, 0.16 mmol) in methylene chloride at 0°C was added diisopropylethylamine (0.18 mL, 1.0 mmol) and benzotriazol-1-yloxyl tris(pyrrolindinyl)phosphonium hexafluorophosphate (PyBOP, 156 mg, 0.30 mmol). After stirring at room temperature for 5 h, the reaction mixture was loaded onto a silica gel chromatography column, and was eluted with hexane/EtOAc (4:1 to 2:1) to give 70 mg of N-(2-phenylbenzoyl)-(L)-4-(2'-cyanophenyl)phenylalanine, methyl ester.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.98-7.2 (17H, m), 4.77 (d, J=9.5, 5.5 Hz), 3.67 (3H, s), 3.19 (1H, dd J= 14, 5.5 Hz), 2.98 (dd, J=14, 9.5 Hz).

Step B. N-(2-Phenylbenzoyl)-(L)-4-(2'-cyanophenyL)phenylalanine.

To a solution of N-(2-phenylbenzoyl)-(L)-4-(2'-cyanophenyl)-phenylalanine, methyl ester (68 mg) in 1.5 mL of methanol/THF/water (1:1:1) at 0°C was added LiOH hydrate (50 mg). After stirring at 0°C for 1 h, 1 mL of hydrochloric acid (1N) was added and the mixture extracted with ethyl acetate (3 X 25 mL). The combined organic fractions were washed with water and brine and dried over anhydrous sodium sulfate. The mixture was filtered, concentrated by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with with hexane/EtOAc/acetic acid (1:1:0.1) to yield N-(2-phenylbenzoyl)-(L)-4-(2'-cyanophenyL)phenylalanine (42 mg) as a white solid.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.6-7.0 (17 H, m), 4.77 (1H, dd, J=9.5, 5.0 Hz), 3.26 (dd, J=14, 5.0 Hz), 3.02 (dd, J=14, 9.5 Hz).

EXAMPLE 17

N-(2-Phenylbenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine.

N-(2-Phenylbenzoyl)-(L)-4-(2'-methoxyphenyL)phenylalanine was prepared by the procedures described in Example 16 substituting (L)-4-(2'-methoxyphenyl)phenylalanine for (L)-4-(2'cyanophenyl)phenylalanine.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.6-6.9 (17H, m), 4.8-4.7 (1H, m), 3.77 (3H, s), 3.22 (1H, dd), 2.96 (1H, dd).

EXAMPLE 18

N-(2-bromo-6-methylbenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine

Step A. 2-Bromo-6-methylbenzoic acid.

Cuprous bromide was added in portions to a hot solution (ca.90°C) of 2-amino-6-methylbenzoic acid (33 mmol, 5 g) in H_2O (80 mL) and HBr (11.5 mL). This was followed by the dropwise addition of a solution of $NaNO_2$ (99 mmol, 6.85 g) in H_2O (20 mL) to this stirred heated solution over a period of 20 min. This mixture was heated at 90°C for one and a half hour and then was heated at reflux for another hour before it was cooled to room temperature and stirred for two hours. The mixture was poured into ice (~100 g), 5% NaOH solution was added until pH 14 was reached and the resulting blue suspension was filtered through celite. The yellow filtrate was acidified with conc. HCl to pH 1. Extractive work-up (EtOAc, 3 x 200 mL) gave a dark yellow residue which was purified by Biotage Flash chromatography over silica gel eluting with 5% MeOH/CH_2Cl_2 to give 4.78g(67%) of the title compound as a brown solid.

500 MHz ($CDCl_3$) δ 2.47 (s, 3H), 7.19-7.23 (m, 2H), 7.45-7.48 (m, 1H).

Mass spectrum (EI) m/e 214.06 $(M + 1)^+$.

Step B. N-(2-Bromo-6-methylbenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine, *t*-butyl ester.

A solution of 4-(2'methoxylphenyl)-L-phenylalanine *t*-butyl ester hydrochloride (65 mg, 0.302 mmol), 2-bromo-6-methylbenzoic acid (110 mg, 0.302 mmol), DIPEA (184 µL, 1.06 mmol) and HBTU (11 5 mg, 0.302 mmol) in DMF (2.5 mL) was stirred for 43 hr at room temperature. The mixture was treated with 5% citric acid, H_2O, and CH_2Cl_2. After separation of the layers, the aqueous layer was washed with CH_2Cl_2 three times. The organic layers were combined and washed with H_2O three times, brine, and then dried with anhydrous $MgSO_4$. The residue obtained after filtration and removal of volatile was purified by prep-plate (1000 micron 20 x 20 cm, Analtech) in 25% EtOAc/Hexanes. The product band was collected, extracted with 10% $MeOH/CH_2Cl_2$, and concentrated to provide 137 mg (86%) of the title compound as a white foam.

500 MHz ($CDCl_3$) δ 1.45 (s, 9H), 2.30 (s, 3H), 3.20-3.31 (m, 2H), 3.81 (s, 3H), 5.10-5.14 (m, 1H), 6.17 (d, J = 8.3 Hz, 2H), 6.98-7.06 (m, 2H), 7.10-7.15 (m, 2H), 7.28-7.44 (m, 5H), 7.46-7.50 (m, 2H).

Mass spectrum (ES) m/e 548.3 $(M+ Na)^+$.

Step C. N-(2-Bromo-6-methylbenzoyl)-(L)-4-(2'-methoxyphenyl)-phenylalanine.

A solution of N-(2-bromo-6-methylbenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine, *t*-butyl ester (131 mg, 0.249 mmol), and TFA (962 µL, 12.4 mmol) in CH_2Cl_2 (7 mL) was stirred overnight at room temperature. A stream of N_2 was applied to remove of TFA/CH_2Cl_2 and the residue was then loaded onto a prep-plate (1000 micron 20 x 20 cm, Analtech) using a minimal amount of CH_2Cl_2. The plate was developed using 95:5:0.5/CH_2Cl_2:MeOH:AcOH and the product band was collected, extracted with 10% $MeOH/CH_2Cl_2$, and concentrated to provide 96 mg (82%) of the title compound as a white solid.

500 MHz (CD_3OD) δ 2.17 (s, 3H), 3.01 (broad s, 1H), 3.37 (broad d, 1H), 3.77 (broad s, 3H), 5.00 (broad s, 1H), 6.96-7.00 (m, 1H), 7.03-7.04 (m, 1H), 7.10-7.15 (m, 2H), 7.27-7.23 (m, 1H), 7.27-7.39 (m, 6H).

Mass spectrum (ES) m/e 470.3 $(M+ 1)^+$.

EXAMPLE 19

N-(2-Pyrroyl)-(L)-4-(2'-methoxyphenyl)phenylalanine

Step A. L-4-iodophenylalanine, *t*-butyl ester hydrochloride

At room temperature, 723 mg (1.62 mmol) of *N*-butoxycarbonyl-L-4-iodophenylalanine (Example 2, Step A) was dissolved in 0.5 mL of anhydrous EtOAc and cooled to 0°C. 4.0 mL of 1N HCl(g)/EtOAc was added dropwise and the ice bath removed 30 minutes after completion of addition. The reaction mixture was allowed to stir at room temperature overnight. TLC (6/1 hexane/EtOAc) indicated substantial residual starting material, therefore another 4.0 mL of 1N HCl(g)/EtOAc was added and the mixture allowed to stir for another 24 h. Volatiles were removed in vacuo and the resulting white powder was dried overnight *in vacuo* at room temperature. This gave 610 mg (98%) of the title compound, homogeneous by TLC (10% MeOH/DCM) which was used in subsequent reactions without further purification.

400 MHz ^{1}H NMR (CD_3OD) δ 1.41(s, 9H),3.11 (d, J = 6.6 Hz, 2H), 4.15 (t, J = 6.6 Hz, 1H), 7.07 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 7.9 Hz, 2H)

Mass spectrum (ESI) *m/e* 348.2 $(M+1)^{+}$.

Step B. *N*-(2-Pyrroyl)-(L)-4-iodophenylalanine *t*-butyl ester

At room temperature, to a solution of 55 mg (0.50 mmol) of pyrrole carboxylic acid in 0.5 mL of DMF was added 75 mg (0.55 mmol) of 1-hydroxybenzotriazole hydrate (HOBt), 128 mg (1.25 mmol) of *N*-methylmorpholine (NMM), and 192 mg (0.50 mmol) of 4-iodophenylalanine *t*-butyl ester hydrochloride. Additional DMF was added as required to keep all components in solution. Subsequently, 115 mg (0.6 mmol) of EDC [1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride] was added and the reaction mixture was allowed to stir at room temperature for 48h. Water was added to quench the reaction and the organic material was extracted 3 times with EtOAc. The organic layers were combined and washed with water twice, brine, and dried (Na_2SO_4). The crude product obtained after filtration and removal of volatiles was flash chromatographed over silica gel to afford 181 mg of the title compound as a foam (homogeneous by TLC in 1/1 hexane/EtOAc; 82% yield).

400 MHz ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.10 (m, 2 H), 4.85 (m, 12H), 6.20 (m, 1H), 6.34 (d J=7.3 Hz, 1H), 6.55 (m, 1H), 6.91 (m, 3H), 7.57 (d, J=7.4 Hz, 2H), . 9.38 (br s, 1H)

Mass spectrum (ESI) *m/e* 441.0 $(M+1)^+$

Step C. *N*-(2-Pyrroyl)-(L)-4-(2'-methoxyphenyl)phenylalanine, *t*-butyl ester.

A mixture of 28 mg (0.183 mmol) of 2-methoxybenzene boronic acid, 0.192 mL of 2.0N aqueous Na_2CO_3 (0.383 mmol), and 0.50 mL of anhydrous ethanol was stirred vigorously at room temperature for 30 minutes. To this slurry was added 67 mg (0.153 mmol) of *N*-(2-Pyrroyl)-(L)-4-iodophenylalanine *t*-butyl ester (obtained from Step C). This mixture was degassed and filled with dry nitrogen three times. 18 mg (0.0153 mmol) of tetrakis(triphenylphosphine)palladium(0) was added and the flask degassed/filled with N_2 twice. The reaction mixture was heated in an oil bath to 60°C for 5h when TLC (2/1 hexane/EtOAc) indicated disappearance of starting material. After being cooled to room temperature, volatiles were removed under reduced pressure and the residue was extracted from 5% $NaHCO_3$(aq) with EtOAc three times. The combined organic layers were washed with water, brine, and dried (Na_2SO_4). The crude product obtained after filtration and removal of solvents was flash chromatographed over silica gel (elution with hexane-EtOAc) to afford 45 mg (70%) of the desired product cleanly (TLC: 1/1 hexane/EtOAc) as an off-white foam. 400 MHz ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.15 (dd, J=13.7, 6.4 Hz, 1 H), 3.22 (dd, J=13.7, 5.2 Hz, 1H), 3.77 (s, 3H), 4.92 (m, 1H), 6.21 (dd, J=6.3, 2.7 Hz, 1H), 6.38 (d J=8.2 Hz, 1H), 6.56 (m, 1H), 6.90-7.05 (m, 3H), 7.22 (d, J=8.1 Hz, 2H), .7.28 (d, J =8.1 Hz, 2H), 7.42 (m, 2H), 9.35 (br s, 1H)

Mass spectrum (ESI) *m/e* 438 $(M+NH_4)^+$.

Step D. *N*-(2-Pyrroyl)-(L)-4-(2'-methoxyphenyl)phenylalanine

At 0°C, to a solution of 40 mg (0.1 mmol) of *N*-(2-Pyrroyl)-(L)-4-(2'-methoxyphenyl)phenylalanine *t*-butyl ester (obtained from Step D) dissolved in 0.050 mL of anhydrous CH_2Cl_2 was added dropwise 0.320 mL of a 1:1 TFA/CH_2Cl_2 solution. After 3 minutes, the ice bath was removed and the pinkish reaction mixture allowed to stirred at room temperature for 2h when TLC's (1/1 hexane/EtOAc) indicated that all starting material had disappeared. The excess TFA was removed by a stream of nitrogen. The residue was taken up in CH_2Cl_2 and methanol and evaporated under reduced pressure and pumped overnight *in vacuo* at room temperature. This crude product was flash chromatographed over silica gel (gradient elution using 2-4-6-9% methanol/CH_2Cl_2) to afford 35 mg of the title compound as a foam (homogeneous by TLC in 10% methanol/CH_2Cl_2; 97% yield).

400 MHz ^1H NMR (CD_3OD) δ 3.15 (m, 1 H), 3.33 (m, 1H), 3.74 (s, 3H), 4.80 (m, 1H), 6.15 (dd, J=3.7, 2.5 Hz, 1H), 6.81 (d, J=2.8 Hz, 1H), 6.89 (dd, J =2.5, 1.3 Hz, 1H), 6.96 (dt, J=7.4, 1.2 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, J=7.5, 1.7Hz, 1H), 7.25-7.30 (m, 3H), 7.37 (d, J=7.2 Hz, 2H), 7.90 (br d, 1H)
Mass spectrum (ESI) *m/e* 365.1 $(M+1)^{+\cdot}$

EXAMPLE 20

N-(2-methylsulfonylbenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine

2-Methylsulfonyl benzoic acid (0.071 g, 0.36 mmol) was reacted with (S)-4-(2'-methoxyphenyl)phenylalanine, t-butyl ester and, following purification, was treated with TFA to give the title compound according to the procedures described in Example 18, Steps B and C.

Characteristic 500 MHz ^1H NMR (CD_3OD) δ 3.15 (dd, 1H); 3.21 (s, 3H); 3.37 (dd, 1H); 3.78 (s, 3H); 4.95 (m, 1H); 6.98 (t, 1H); 7.08 (d, 1H); 7.25 (d, 1H); 7.28 (t, 1H); 7.35 (d, 2H); 7.41 (m, 3H); 7.61-7.73 (m, 2H); 8.05 (d, 1H).
Mass Spectrum: Calc. $C_{24}H_{23}NO_6S$; 453; Obs: 454 $(M+1)^+$.

EXAMPLE 21

N-(2-Phenylthiobenzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine

2-Thiophenyl benzoic acid (0.15 g, 0.65 mmol) was reacted with (S)-4-(2'-methoxyphenyl)phenylalanine, t-butyl ester and, following purification, was treated with TFA to give the title compound according to the procedures described in Example 18, Steps B and C.

Characteristic 500 MHz ^1H NMR (CD_3OD) δ 3.10 (dd, 1H); 3.35 (dd, 1H); 3.65 (s, 3H); 4.90 (m, 1H); 6.91 (t, 1H); 7.00 (d, 1H); 7.05 (d, 1H); 7.15 (d, 1H); 7.20-7.40 (m, 13H).
Mass spectrum: Calc. $C_{29}H_{25}NO_4S$; 483; Obs: 484 $(M+1)^+$.

EXAMPLE 22

N-(2-phenylsulfonyl-1-benzoyl)-(L)-4-(2'-methoxyphenyl)phenylalanine.

The tert-butyl ester from Example 21 (0.25 g, 0.46 mmol) was treated with meta-chloroperbenzoic acid (MCPBA, 0.29 g, 1.16 mmol) in CH_2Cl_2 (2.5 mL) and stirred overnight. The reaction mixture was diluted EtOAc and washed with

saturated aqueous sodium bisulfite solution (2x), sodium bicarbonate solution (2x), brine (1x), dried over anhydrous magnesium sulfate and concentrated. Following purification by preparative thin layer chromatography on silica (1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes), the ester was treated with TFA to give the desired product as described in Example 18, Step C.

Characteristic 500 MHz ^1H NMR (CD_3OD) δ 3.19 (dd, 1H); 3.36 (dd, 1H); 3.72 (s, 3H); 4.97 (m, 1H); 6.95 (t, 1H); 7.02 (d, 1H); 7.20-7.35 (m, 3H); 7.39 (d, 2H); 7.42 (d, 2H); 7.50-7.57 (m, 2H); 7.59-7.61 (m, 3H); 8.00 (d, 2H); 8.06 (m, 1H).

Mass spectrum: Calc. $C_{29}H_{25}NO_6S$; 515; Obs: 516 $(M+1)^+$.

EXAMPLE 23

Inhibition of VLA-4 Dependent Adhesion to BSA-CS-1 Conjugate

Step A. Preparation of CS-1 Coated Plates.

Untreated 96 well polystyrene flat bottom plates were coated with bovine serum albumin (BSA; 20 mg/ml) for 2 hours at room temperature and washed twice with phosphate buffered saline (PBS). The albumin coating was next derivatized with 10 mg/ml 3-(2-pyridyldithio) propionic acid N-hydroxysuccinimide ester (SPDP), a heterobifunctional crosslinker, for 30 minutes at room temperature and washed twice with PBS. The CS-1 peptide (Cys-Leu-His-Gly-Pro-Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr), which was synthesized by conventional solid phase chemistry and purified by reverse phase HPLC, was next added to the derivatized BSA at a concentration of 2.5 mg/ml and allowed to react for 2 hours at room temperature. The plates were washed twice with PBS and stored at 4°C.

Step B. Preparation of Fluorescently Labeled Jurkat Cells.

Jurkat cells, clone E6-1, obtained from the American Type Culture Collection (Rockville, MD; cat # ATCC TIB-152) were grown and maintained in RPMI-1640 culture medium containing 10% fetal calf serum (FCS), 50 units/ml penicillin, 50 mg/ml streptomycin and 2 mM glutamine. Fluorescence activated cell sorter analysis with specific monoclonal antibodies confirmed that the cells expressed both the α4 and β1 chains of VLA-4. The cells were centrifuged at 400xg for five minutes and washed twice with PBS. The cells were incubated at a concentration of 2

x 10^6 cells/ml in PBS containing a 1 mM concentration of a fluorogenic esterase substrate (2', 7'-bis-(2-carboxyethyl)-5-(and -6)-carboxyfluorescein, acetoxymethyl ester; BCECF-AM; Molecular Probes Inc., Eugene, Oregon; catalog #B-1150) for 30-60 minutes at 37°C in a 5% CO_2/air incubator. The fluorescently labeled Jurkat cells were washed two times in PBS and resuspended in RPMI containing 0.25% BSA at a final concentration of 2.0 x 10^6 cells/ml.

Step C. Assay Procedure.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 mM. Three mL of diluted compound, or vehicle alone, were premixed with 300 mL of cell suspension in 96-well polystyrene plates with round bottom wells. 100 mL aliquots of the cell /compound mixture were then transferred in duplicate to CS-1 coated wells. The cells were next incubated for 30 minutes at room temperature. The non-adherent cells were removed by two gentle washings with PBS. The remaining adherent cells were quantitated by reading the plates on a Cytofluor II fluorescence plate reader (Perseptive Biosystems Inc., Framingham, MA; excitation and emission filter settings were 485 nm and 530 nm, respectively). Control wells containing vehicle alone were used to determine the level of cell adhesion corresponding to 0% inhibition. Control wells coated with BSA and crosslinker (no CS-1 peptide) were used to determine the level of cell adhesion corresponding to 100% inhibition. Cell adhesion to wells coated with BSA and crosslinker was usually less than 5% of that observed to CS-1 coated wells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

EXAMPLE 24

Antagonism of VLA-4 Dependent Binding to VCAM-Ig Fusion Protein.

Step A. Preparation of VCAM-Ig.

The signal peptide as well as domains 1 and 2 of human VCAM (GenBank Accession no. M30257) were amplified by PCR using the human VCAM cDNA (R & D Systems) as template and the following primer sequences:

3'-PCR primer:

5'-AATTATAATTTGATCAACTTACCTGTCAATTCTTTTACAGCCTGCC-3';

5'-PCR primer:

5'-ATAGGAATTCCAGCTGCCACCATGCCTGGGAAGATGGTCG-3'.

The 5'-PCR primer contained EcoRI and PvuII restriction sites followed by a Kozak consensus sequence (CCACC) proximal to the initiator methionine ATG. The 3'-PCR primer contained a BclI site and a splice donor sequence. PCR was performed for 30 cycles using the following parameters: 1 min. at 94°C, 2 min. at 55°C, and 2 min. at 72°C. The amplified region encoded the following sequence of human VCAM-1:

MPGKMVVILGASNILWIMFAASQAFKIETTPESRYLAQIGDSVSLTCSTTGCES PFFSWRTQIDSPLNGKVTNEGTTSTLTMNPVSFGNEHSYLCTATCESRKLEKGI QVEIYSFPKDPEIHLSGPLEAGKPITVKCSVADVYPFDRLEIDLLKGDHLMKSQ EFLEDADRKSLETKSLEVTFTPVIEDIGKVLVCRAKLHIDEMDSVPTVRQAVK EL. The resulting PCR product of 650 bp was digested with EcoRI and BclI and ligated to expression vector pIg-Tail (R & D Systems, Minneapolis, MN) digested with EcoRI and BamHI. The pIg-Tail vector contains the genomic fragment which encodes the hinge region, CH2 and CH3 of human IgG1 (GenBank Accession no. Z17370). The DNA sequence of the resulting VCAM fragment was verified using Sequenase (US Biochemical, Cleveland, OH). The fragment encoding the entire VCAM-Ig fusion was subsequently excised from pIg-Tail with EcoRI and NotI and ligated to pCI-neo (Promega, Madison, WI) digested with EcoRI and NotI. The resulting vector, designated pCI-neo/VCAM-Ig was transfected into CHO-K1 (ATCC CCL 61) cells using calcium-phosphate DNA precipitation (Specialty Media, Lavalette, NJ). Stable VCAM-Ig producing clones were selected according to standard protocols using 0.2-0.8 mg/ml active G418 (Gibco, Grand Island, NY), expanded, and cell supernatants were screened for their ability to mediate Jurkat adhesion to wells previously coated with 1.5 mg/ml (total protein) goat anti-human IgG (Sigma, St. Louis, MO). A positive CHO-K1/VCAM-Ig clone was subsequently adapted to CHO-SFM serum-free media (Gibco) and maintained under selection for stable expression of VCAM-Ig. VCAM-Ig was purified from crude culture

supernatants by affinity chromatography on Protein A/G Sepharose (Pierce, Rockford, IL) according to the manufacturer's instructions and desalted into 50 mM sodium phosphate buffer, pH 7.6, by ultrafiltration on a YM-30 membrane (Amicon, Beverly, MA).

Step B. Preparation of ^{125}I-VCAM-Ig.

VCAM-Ig was labeled to a specific radioactivity greater that 1000 Ci/mmole with ^{125}I-Bolton Hunter reagent (New England Nuclear, Boston, MA; cat # NEX120-0142) according to the manufacturer's instructions.The labeled protein was separated from unincorporated isotope by means of a calibrated HPLC gel filtration column (G2000SW; 7.5 x 600 mm; Tosoh, Japan) using uv and radiometric detection.

Step C. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 µM. Jurkat cells were centrifuged at 400xg for five minutes and resuspended in binding buffer (25 mM HEPES, 150 mM NaCl, 3 mM KCl, 2 mM glucose, 0.1% bovine serum albumin, pH 7.4). The cells were centrifuged again and resuspended in binding buffer supplemented with $MnCl_2$ at a final concentration of 1 mM. Compounds were assayed in Millipore MHVB multiscreen plates (cat# MHVBN4550, Millipore Corp., MA) by making the following additions to duplicate wells: (i) 200 µL of binding buffer containing 1 mM $MnCl_2$; (ii) 20 µL of ^{125}I-VCAM-Ig in binding buffer containing 1 mM $MnCl_2$ (final assay concentration ~ 100 pM); (iii) 2.5 µL of compound solution or DMSO; (iv) and 0.5 x 10^6 cells in a volume of 30 mL. The plates were incubated at room temperature for 30 minutes, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 µL of binding buffer containing 1 mM $MnCl_2$. After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat# 6005178), 100 µL of Microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition. Contol wells in which cells were omitted were used to determine the level of binding

corresponding to 100% inhibition. Binding of ^{125}I-VCAM-Ig in the absence of cells was usually less than 5% of that observed using cells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

EXAMPLE 25

Antagonism of $\alpha_4\beta_7$ Dependent Binding to VCAM-Ig Fusion Protein.

Step A. $\alpha_4\beta_7$ Cell line.

RPMI-8866 cells (a human B cell line $\alpha_4^+\beta_1^-\beta_7^+$; a gift from Prof. John Wilkins, University of Manitoba, Canada) were grown in RPMI/10% fetal calf serum/ 100 U penicillin/100 μg streptomycin/2 mM L-glutamine at 37°C, 5 % carbon dioxide. The cells were pelleted at 1000 rpm for 5 minutes and then washed twice and resuspended in binding buffer (25 mM Hepes, 150 mM NaCl , 0.1 % BSA, 3 mM KCl, 2 mM Glucose, pH 7.4).

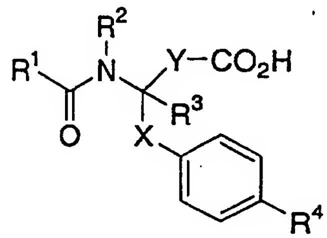
Step B. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μM. Compounds were assayed in Millipore MHVB multiscreen plates (Cat# MHVBN4550) by making the following sequential additions to duplicate wells: (i) 100 ml/well of binding buffer containing 1.5 mM $MnCl_2$; (ii) 10 ml/well ^{125}I-VCAM-Ig in binding buffer (final assay concentration < 500 pM); (iii) 1.5 ml/well test compound or DMSO alone; (iv) 38 ml/well RPMI-8866 cell suspension (1.25 x 10^6 cells/well). The plates were incubated at room temperature for 45 minutes on a plate shaker at 200 rpm, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 mL of binding buffer containing 1 mM $MnCl_2$. After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat# 6005178), 100 mL of Microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition. Wells in which cells were omitted were used to determine the level of

binding corresponding to 100% inhibition. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

WHAT IS CLAIMED IS:

1. A method for the prevention or treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mamal an effective amount of a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof wherein:

R^1 is
1) aryl,
2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^2 is
1) hydrogen,
2) C_{1-10}alkyl,
3) C_{2-10}alkenyl,
4) C_{2-10}alkynyl,
5) C_{3-7}cycloalkyl,
6) aryl,
7) heteroaryl,

wherein alkyl, alkenyl, alkynyl are optionally substituted with one to four substituents independently selected from R^a; cycloalkyl, aryl, and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^3 is
1) hydrogen,
2) C_{1-10}alkyl,
3) C_{2-10}alkenyl,
4) C_{2-10}alkynyl,

5) aryl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^a, and aryl is optionally substituted with one to four substituents independently selected from R^a,

R^4 is
1) hydrogen,
2) C1-10alkyl,
3) hydroxy,
4) C1-10alkoxy,
5) Z-R^1,
6) C_{2-10}alkenyl,
7) C_{2-10}alkynyl,
8) -$O(CR^fR^g)_nNR^dR^e$,
9) -$OC(O)R^d$,
10) -$OC(O)NR^dR^e$,
11) -$S(O)_mR^d$,
12) -$S(O)_2OR^d$,
13) -$S(O)_mNR^dR^e$,
14) -$C(O)R^d$,
15) -CO_2R^d,
16) -$C(O)NR^dR^e$,

wherein alkyl, alkenyl, alkynyl and alkoxy are optionally substituted with one to four substituents selected from R^a;

R^a is
1) aryl,
2) -OR^d,
3) -NO_2,
4) halogen
5) -$S(O)_mR^d$,
6) -SR^d,
7) -$S(O)_2OR^d$,
8) -$S(O)_mNR^dR^e$,
9) -NR^dR^e,
10) -$O(CR^fR^g)_nNR^dR^e$,

11) $-C(O)R^d$,
12) $-CO_2R^d$,
13) $-CO_2(CR^fR^g)_nCONR^dR^e$,
14) $-OC(O)R^d$,
15) -CN,
16) $-C(O)NR^dR^e$,
17) $-NR^dC(O)R^e$,
18) $-OC(O)NR^dR^e$,
19) $-NR^dC(O)OR^e$,
20) $-NR^dC(O)NR^dR^e$,
21) $-CR^d(N-OR^e)$,
22) CF_3,
23) $-OCF_3$, or
24) heteroaryl;

R^b is
1) a group selected from R^a,
2) C_{1-10} alkyl,
3) C_{2-10} alkenyl,
4) C_{2-10} alkynyl,
5) aryl C_{1-10}alkyl,
6) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

R^c is
1) halogen,
2) amino,
3) carboxy,
4) C_{1-4}alkyl,
5) C_{1-4}alkoxy,
6) aryl,
7) aryl C_{1-4}alkyl,
8) hydroxy,
9) CF_3, or
10) aryloxy;

R^d and R^e are independently selected from hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, Cy and Cy C_{1-10}alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from R^c; or

R^d and R^e together with the nitrogen atom to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C_{1-10}alkyl, Cy and Cy-C_{1-10}alkyl; or

R^f and R^g together with the carbon atom to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from N, O and S;

Cy is independently selected from cycloalkyl, heterocyclyl, aryl, or heteroaryl;

m is an integer from 1 to 2;

n is an integer from 1 to 10;

X and Y are independently a bond or C_{1-2}alkylene;

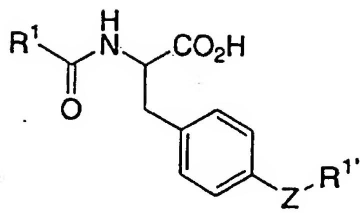
Z is
1) a bond,
2) O,
3) $S(O)_m$,
4) C_{1-10}alkylene,

or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein said disease or disorder is selected from asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, and inflammatory bowel disease.

3. A method for preventing the action of VLA-4 in a mammal which comprises administering to said mammal a thereapeutically effective amount of a compound of formula I.

4. A compound of the formula Ia:



Ia

wherein R^1 and $R^{1'}$ are independently selected from

1) aryl,
2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R^b;

R^b is independently selected from:

1) aryl,
2) $-OR^d$,
3) $-NO_2$,
4) halogen
5) $-S(O)_mR^d$,
6) $-SR^d$,
7) $-S(O)_2OR^d$,
8) $-S(O)_mNR^dR^e$,
9) $-NR^dR^e$,
10) $-O(CR^fR^g)_nNR^dR^e$,
11) $-C(O)R^d$,
12) $-CO_2R^d$,
13) $-CO_2(CR^fR^g)_nCONR^dR^e$,
14) $-OC(O)R^d$,
15) -CN,
16) $-C(O)NR^dR^e$,
17) $-NR^dC(O)R^e$,
18) $-OC(O)NR^dR^e$,
19) $-NR^dC(O)OR^e$,
20) $-NR^dC(O)NR^dR^e$,
21) $-CR^d(N-OR^e)$,

22) CF_3,
23) $-OCF_3$,
24) heteroaryl
25) C_{1-10} alkyl,
26) C_{2-10} alkenyl,
27) C_{2-10} alkynyl,
28) aryl C_{1-10}alkyl,
29) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

R^c is
1) halogen,
2) amino,
3) carboxy,
4) C_{1-4}alkyl,
5) C_{1-4}alkoxy,
6) aryl,
7) aryl C_{1-4}alkyl,
8) hydroxy,
9) CF_3, or
10) aryloxy;

R^d and R^e are independently selected from hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, Cy and Cy C_{1-10}alkyl, wherein alkyl, alkenyl, alkynyl and Cy are optionally substituted with one to four substituents independently selected from R^c; or

R^d and R^e together with the nitrogen atom to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C_{1-10}alkyl, Cy and Cy-C_{1-10}alkyl; or

R^f and R^g together with the carbon atom to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from N, O and S;

Cy is independently selected from cycloalkyl, heterocyclyl, aryl, or heteroaryl;

Z is
1) a bond,
2) O,

3) $S(O)_m$,

4) C_{1-10}alkylene,

m is an integer from 1 to 2;

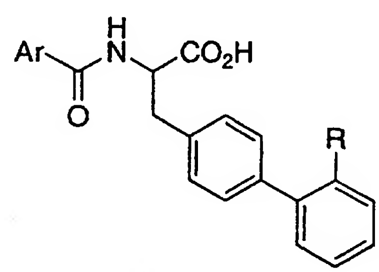
n is an integer from 1 to 10;

or a pharmaceutically acceptable salt thereof.

5. A compound of Claim 4 wherein R^1 is phenyl or a heteroaryl selected from the group consisting of furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyrimidinyl, and pyridyl, each of the phenyl and heteroaryl is optionally substituted with 1 or 2 groups independently selected from OR^d, halogen, C_{1-3}alkyl optionally substituted with a group selected from R^c, $S(O)_mR^d$ and SR^d.

6. A compound of Claim 4 wherein Z is a bond and $R^{1'}$ is phenyl bearing a substituent at the atom adjacent to the atom connected to Z.

7. A compound of claim 4 selected from the group consisting of:



Ar	**R**
Ph	CN
Ph	OCH_3
2-furyl	CN
3-furyl	CN
2-OCH_3-Ph	CN
3-OCH_3-Ph	CN
4-OCH_3-Ph	CN
2-pyridyl	CN
2-pyridyl	OCH_3

6-OH-2-pyridyl	CN
3-CH_3-2-thienyl	CN
4-NH_2CH_2-Ph	CN
2-Ph-Ph	CN
2-Ph-Ph	OCH_3
2-Br-6-CH_3-Ph	OCH_3
2-pyrrolyl	OCH_3
2-CH_3SO_2-Ph	OCH_3
2-PhS-Ph	OCH_3
2-$PhSO_2$-Ph	OCH_3

8. A pharmaceutical composition which comprises a compound of formula I and a pharmaceutically acceptable carrier.

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SS

INVESTOR IN PEOPLE

Application No: GB 0017279.1

Examiner: Dr Fatema Sardharwala

Claims searched: 1-8

Date of search: 10 January 2001

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S): A5B (BHA)

Int Cl (Ed.7): A61K 31/19, 31/195

Other: EPODOC, WPI, JAPIO, CAPLUS

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X, P	WO 99/36393 A1	(TANABE SEIYAKU) whole document, see esp. all Examples (starting page 61) e.g. Example 82	1-8
A	WO 99/37618 A1	(CELLTECH)	
X	WO 99/26922 A1	(MERCK) whole document, see esp. Examples	1-6, 8
X	WO 98/53817 A1	(MERCK) whole document, see esp. Examples	1-6, 8

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
		E	Patent document published on or after, but with priority date earlier than, the filing date of this application.
&	Member of the same patent family		